


 Cite this: *Chem. Commun.*, 2020, 56, 12664

## Comment on "Investigation of Zr(IV) and <sup>89</sup>Zr(IV) complexation with hydroxamates: progress towards designing a better chelator than desferrioxamine B for immuno-PET imaging" by F. Guérard, Y.-S. Lee, R. Tripier, L. P. Szajek, J. R. Deschamps and M. W. Brechbiel, *Chem. Commun.*, 2013, 49, 1002†

 Antonio Bianchi \* and Matteo Savastano \*

 Received 14th February 2020,  
Accepted 10th September 2020

DOI: 10.1039/d0cc01189d

[rsc.li/chemcomm](http://rsc.li/chemcomm)

An alternative analysis of the complexes formed by Zr(IV) with acetohydroxamate shows that, in comparison with the results reported in the title article, a more complicated complexation model is found, the stability constants of the common complexes are considerably different and complexation of Zr(IV) does not show any unusual behaviour.

The title article<sup>1</sup> reported the crystal structure of the tetra-chelated Zr(IV) complex Zr(Me-AHA)<sub>4</sub> (Me-AHA = *N*-methyl acetohydroxamate) along with the investigation of the solution structures, performed by means of DFT calculations, and the determination of the stability constants of the complexes formed in solution by Me-AHA and its non-methylated analogue AHA (acetohydroxamate). The crystal structure of Zr(Me-AHA)<sub>4</sub>, showing Zr(IV) surrounded by four hydroxamates, evoked the accessibility to a single ligand containing four hydroxamate groups that is expected to be a better Zr(IV) chelator than desferrioxamine B (DFO), a siderophore containing three hydroxamates which is currently used for antibody radiolabeling with <sup>89</sup>Zr in nuclear medicine.

We recently came across the title article while we were performing a study dealing with the speciation of the Zr(IV) complexes with DFO in aqueous solution.<sup>2</sup> The crystal structure of the Zr(Me-AHA)<sub>4</sub> complex is a key reference for the structure of hydroxamate complexes with Zr(IV). While the structural study in this paper appears to us of high quality and very interesting, the stability constants of the Zr(IV) complexes therein reported left us somewhat perplexed. According to this paper, Zr(IV) can bind four AHA and Me-AHA ligands in successive steps for which the following equilibrium constants  $\log K_n = \frac{[\text{ML}_n]}{[\text{ML}_{n-1}][\text{L}]}$  (L = AHA, Me-AHA,  $n = 1-4$ , charges of ligands

and complexes omitted through the text) were determined: for AHA  $\log K_1 = 12.01$ ,  $\log K_2 = 11.99$ ,  $\log K_3 = 5.69$ ,  $\log K_4 = 15.38$ ; for Me-AHA  $\log K_1 = 13.21$ ,  $\log K_2 = 12.01$ ,  $\log K_3 = 3.44$ ,  $\log K_4 = 17.32$ . The ground of our first perplexity was the enormous constants of the fourth equilibria ( $n = 4$ ) that exceed all the other ones, being up to  $10^{10}/10^{14}$  times higher than the third ones. Instead, a steady decrease of  $K_n$  values with increasing  $n$  would be normal, except for the very few cases in which the metal–ligand bond energies change drastically as a function of  $n$ . There are several reasons for this general trend, including statistical factors, steric hindrance of the ligands if they are bulkier than the replaced water molecules and electrostatic factors that are very important for charged ligands.<sup>3</sup> Among the rare cases in which this trend undergoes an inversion at a certain value of  $n$ , there are the complexes of Fe(II) with 1,10-phenanthroline and 2,2'-bipyridine as a consequence of the large stabilization occurring for this d<sup>6</sup> cation when the coordination of the third ligand molecule transform the high spin bis-chelate complexes into the low spin tris-chelate ones.<sup>4</sup> The steady decrease trend should instead be followed by Zr(IV), which has no d electrons, especially when it forms complexes with charged ligands like AHA and Me-AHA. As a matter of fact, this trend is followed by AHA and Me-AHA complexes with several divalent and trivalent transition metal ions,<sup>5</sup> though they are not d<sup>0</sup>.

The experimental conditions adopted to determine the stability constants of the ZrL<sub>*n*</sub> ( $n = 1-4$ ) complexes, reported in the title article, were another source of perplexity, since all measurements were performed by using solutions containing Zr(IV) and L in the 1 : 4 molar ratio; one might suspect that low

Department of Chemistry "Ugo Schiff", University of Florence, Italy.

E-mail: antonio.bianchi@unifi.it, matteo.savastano@unifi.it

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0cc01189d

substituted species such as ZrL and ZrL<sub>2</sub> are unlikely to form under such conditions. Indeed, the distribution diagrams of the complex species formed by AHA and Me-AHA (see ESI† of the title article) show that the ZrL<sub>4</sub> complexes were practically the only species present in the experimental solutions, apart from the Zr(OH)<sub>4</sub> complex that becomes prevalent in very alkaline media. ZrL and ZrL<sub>2</sub> are formed in less than 5% while ZrL<sub>3</sub> is not formed at all. It is intuitive, but it can also be proved mathematically,<sup>6</sup> that the stability constant of a complex in solution can be determined by pH-metric methods only in the case this complex affects the solution pH, which requires it is formed in appreciable amounts.

Furthermore, it seems somewhat surprising that a metal ion which forms highly hydrolysed species in solution, such as Zr(OH)<sub>4</sub>, gives rise with AHA and Me-AHA only to complexes of the type ZrL<sub>n</sub> (*n* = 1–4), none of which undergoes hydrolysis. In other words, it seems somewhat surprising that the coordination of a single AHA or Me-AHA bidentate ligand is enough for Zr(OH)<sub>4</sub> to release all four OH<sup>−</sup> anions. As a matter of fact, AHA does form hydroxylated complexes with other metal ions, such as Ni(II), Cu(II) and Zn(II),<sup>5</sup> which are less prone than Zr(IV) to hydrolyse.

Then, considering the relevance of hydroxamate complexes of Zr(IV) for nuclear medicine, we thought it would be useful to verify the equilibrium data reported in the title article. To do this, six potentiometric (pH-metric) titrations were performed on AHA/Zr(IV) aqueous solutions, by using already described equipment and methodology,<sup>7</sup> and exploring Zr(IV):AHA molar ratios ranging from 1:1 to 1:8 in the pH range 2.3–11.2 (0.1 M Me<sub>4</sub>NCl, 298.1 K, experimental details are given in the ESI†). A preliminary analysis of this set of potentiometric data by means of the HYPERQUAD<sup>8</sup> computer program showed that curves fitting was not possible by using a model composed exclusively of the ZrL<sub>n</sub> (*n* = 1–4) complexes. Introduction of hydroxylated species of ZrL<sub>n</sub> (*n* = 1–4) complexes led to a good fitting of the acidic branches of the potentiometric curves and to inclusion of [Zr(AHA)OH]<sup>2+</sup> and [Zr(AHA)(OH)<sub>2</sub>]<sup>+</sup> into the speciation model. Tentative to introduce further mononuclear hydroxylated species did not help to fit the alkaline branches of the curves. On the contrary, a complete and satisfactory fitting of the six curves, over the entire pH range, was achieved with the introduction of the trinuclear hydroxylated species [Zr<sub>3</sub>(AHA)<sub>3</sub>(OH)<sub>7</sub>]<sup>2+</sup> and [Zr<sub>3</sub>(AHA)<sub>3</sub>(OH)<sub>8</sub>]<sup>+</sup>. Alternatively, satisfactory fittings can also be obtained by introducing the hexanuclear species [Zr<sub>6</sub>(AHA)<sub>6</sub>(OH)<sub>14</sub>]<sup>4+</sup> and [Zr<sub>6</sub>(AHA)<sub>6</sub>(OH)<sub>16</sub>]<sup>2+</sup>, or higher order oligomers, with no modification, within experimental errors, of the stability constants of the other complexes (see ESI†). Interestingly, these species are reminiscent of the Zr<sub>3</sub> and Zr<sub>6</sub> clusters found in hydroxylated complexes of Zr(IV) containing bridging chelate ligands and bridging (μ<sub>2</sub>, μ<sub>3</sub>) hydroxide anions.<sup>9</sup>

The best fitting model (comprising [Zr<sub>3</sub>(AHA)<sub>3</sub>(OH)<sub>7</sub>]<sup>2+</sup> and [Zr<sub>3</sub>(AHA)<sub>3</sub>(OH)<sub>8</sub>]<sup>+</sup>) and the stability constants of the relative complexes are reported in Table 1. According to the new equilibrium data, AHA coordination to Zr(IV) does not show any special behaviour, the binding of successive AHA ligand molecules following the expected trend of decreasing equilibrium constants, in analogy with the behaviour previously found for other metal ions such as Ni(II), Zn(II) and Fe(III) (Fig. 1).

Table 1 Equilibrium constants for the formation of Zr(IV) complexes with AHA. 0.1 M Me<sub>4</sub>NCl, 298.1 K

Equilibria	log <i>K</i>
Zr <sup>4+</sup> + AHA <sup>−</sup> = [ZrAHA] <sup>3+</sup>	14.57(9) <sup>a</sup>
[ZrAHA] <sup>3+</sup> + AHA <sup>−</sup> = [Zr(AHA) <sub>2</sub> ] <sup>2+</sup>	11.9(2)
[Zr(AHA) <sub>2</sub> ] <sup>2+</sup> + AHA <sup>−</sup> = [Zr(AHA) <sub>3</sub> ] <sup>+</sup>	9.0(2)
[Zr(AHA) <sub>3</sub> ] <sup>+</sup> + AHA <sup>−</sup> = [Zr(AHA) <sub>4</sub> ]	4.5(1)
Zr <sup>4+</sup> + AHA <sup>−</sup> + H <sub>2</sub> O = [Zr(AHA)OH] <sup>2+</sup> + H <sup>+</sup>	12.77(8)
Zr <sup>4+</sup> + AHA <sup>−</sup> + 2H <sub>2</sub> O = [Zr(AHA)(OH) <sub>2</sub> ] <sup>+</sup> + 2H <sup>+</sup>	10.68(8)
3Zr <sup>4+</sup> + 3AHA <sup>−</sup> + 8H <sub>2</sub> O = [Zr <sub>3</sub> (AHA) <sub>3</sub> (OH) <sub>8</sub> ] <sup>+</sup> + 8H <sup>+</sup>	23.21(5)
3Zr <sup>4+</sup> + 3AHA <sup>−</sup> + 7H <sub>2</sub> O = [Zr <sub>3</sub> (AHA) <sub>3</sub> (OH) <sub>7</sub> ] <sup>2+</sup> + 7H <sup>+</sup>	31.8(1)

<sup>a</sup> Values in parentheses are standard deviations.

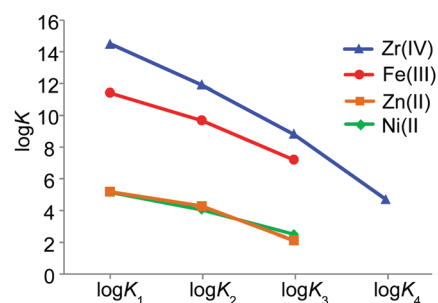


Fig. 1 Logarithms of the equilibrium constants for the addition of successive AHA ligand to metal ions in water. Values for Ni(II), Zn(II) and Fe(III) are from ref. 5.

Furthermore, Fig. 1 shows that a normal trend of increasing stability with increasing metal ion charge applies to the equally substituted AHA complexes of these metal cations.

In conclusion, the new data, obtained in compliance of recommended rules for the determination of stability constants,<sup>6,10–12</sup> offer an alternative speciation of the complexes formed by Zr(IV) with AHA, show that this metal ion has no special properties in the formation of hydroxamate complexes, confirm that it is able to bind four hydroxamate groups in solution, although with a normal decreasing ability in the successive steps, and confirm that potentiometry, when adequately used, can be a good method for studying complexation equilibria of even challenging metal cations such as Zr(IV). The new equilibrium data complement the key structural information reported in the title article.

This contribution is based upon work from COST Action CA18202, NECTAR – Network for Equilibria and Chemical Thermodynamics Advanced Research, supported by COST (European Cooperation in Science and Technology).

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- 1 F. Guérard, Y.-S. Lee, R. Tripier, L. P. Szajek, J. R. Deschamps and M. W. Brechbiel, *Chem. Commun.*, 2013, **49**, 1002–1004.
- 2 M. Savastano, C. Bazzicalupi, G. Ferraro, E. Fratini, P. Gratteri and A. Bianchi, *Molecules*, 2019, **24**, 2098.

- 3 F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, John Wiley & Sons, New York, 5th edn, 1988.
- 4 H. Irving and D. H. Mellor, *J. Chem. Soc.*, 1962, 5222–5237.
- 5 B. Kurzak, H. Kozłowski and E. Farkas, *Coord. Chem. Rev.*, 1992, **114**, 169–200.
- 6 H. S. Rossoti, *Talanta*, 1974, **21**, 809–829.
- 7 C. Bazzicalupi, A. Bianchi, T. Biver, C. Giorgi, S. Santarelli and M. Savastano, *Inorg. Chem.*, 2014, **53**, 12215–12224.
- 8 P. Gans, A. Sabatini and A. Vacca, *Talanta*, 1996, **43**, 1739–1753.
- 9 B. Nateghi, I. Boldog, K. V. Domasevitch and C. Janiak, *CrystEngComm*, 2018, **20**, 5132–5136, and references therein cited.
- 10 L. G. Sillén, *J. Inorg. Nucl. Chem.*, 1958, **8**, 176–195.
- 11 G. H. Nancollas and M. B. Tomson, *Pure Appl. Chem.*, 1982, **54**, 2675–2692.
- 12 A. Braibanti, G. Ostacoli, P. Paoletti, L. D. Petitt and S. Sammartano, *Pure Appl. Chem.*, 1987, **59**, 1721–1728.